Studies on the Total Synthesis of Lactonamycin: Construction of Model ABCD Ring Systems

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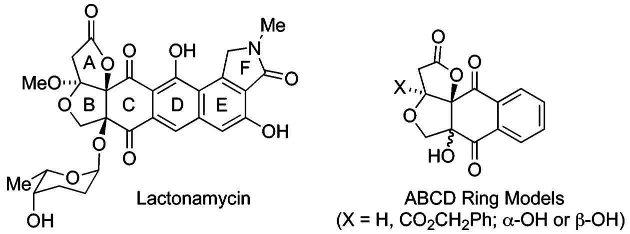

Model studies on the synthesis of the tetracyclic ABCD ring system of lactonamycin (**1**) are described. The key step involved the double Michael addition reaction of alcohol **8** to propynoate esters to produce the BCD units **13** and **14** of the target **1**. Alternatively, double Michael addition of alcohol **8** to di-*tert*-butyl acetylenedcarboxylate gave the corresponding BCD ring systems **36** and **37**. Acid-mediated hydrolysis of the dihydroquinone monoketal units of **13** and **14** and **36** and **37** in the presence of air gave the corresponding quinones **7** and **39**. These were converted into the tetracyclic ABCD units **6**, **26a**, **40**, and **42** of lactonamycin (**1**) by either dihydroxylation or epoxidation and acid-catalyzed lactonization.

Introduction

Lactonamycin(**1**)[1] and the recently isolated derivative lactonamycin-Z (**2**)[2] have intriguing structural features that include a naphtho[*e*]isoindole ring system on the east side (EF-rings) and a densely oxygenated fused perhydrofuran−furanone ring system containing a labile tertiary methoxy group on the west side (AB-rings) (Figure 1). The natural products also each contain a 2-deoxy sugar unit (**1**, α-L-rhodinopyranose; **2**, α-L-2,6-dideoxyribopyranose) attached through a tertiary α-keto-glycosidic linkage. Lactonamycin (**1**) shows significant levels of antimicrobial activity toward Gram-positive bacteria, being especially active against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). In addition, lactonamycin (**1**) shows significant levels of cytotoxicity against various tumor cell lines.[3]

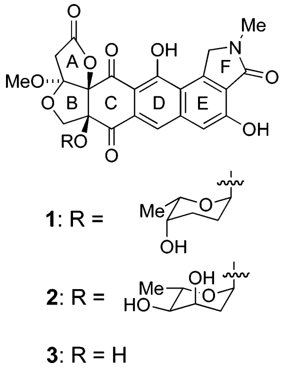

FIGURE 1. Structures of lactonamycin (**1**), lactonamycin-Z (**2**), and lactonamycinone (**3**).

Three groups have reported synthetic studies directed toward the total synthesis of lactonamycin (**1**). Two different routes for the construction of model ABCD ring systems were reported by Danishefsky and Cox,[4] and the Danishefsky group followed

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(1) Matsumoto, N.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276 and references therein.

(2) Holtzel, A.; Dieter, A.; Schmid Dietmar, G.; Brown, R.; Goodfellow, M.; Beil, W.; Jung, G.; Fiedler, H.-P. *J. Antibiot.* **2003**, *56*, 1058.

(3) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 269.

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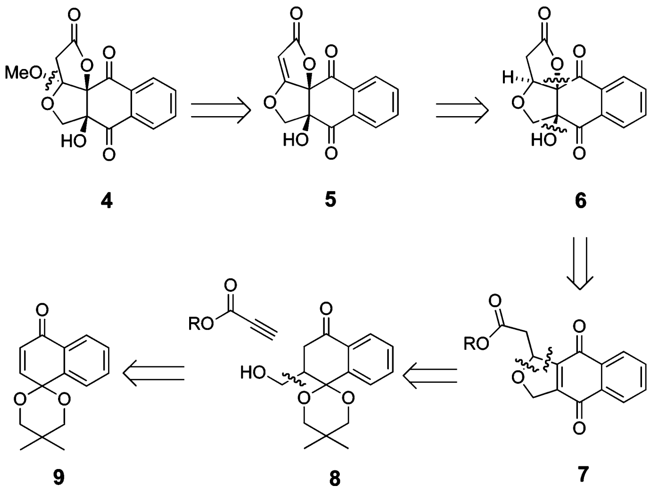
SCHEME 1. Retrosynthetic Analysis of the Model ABCD Tetracyclic Target



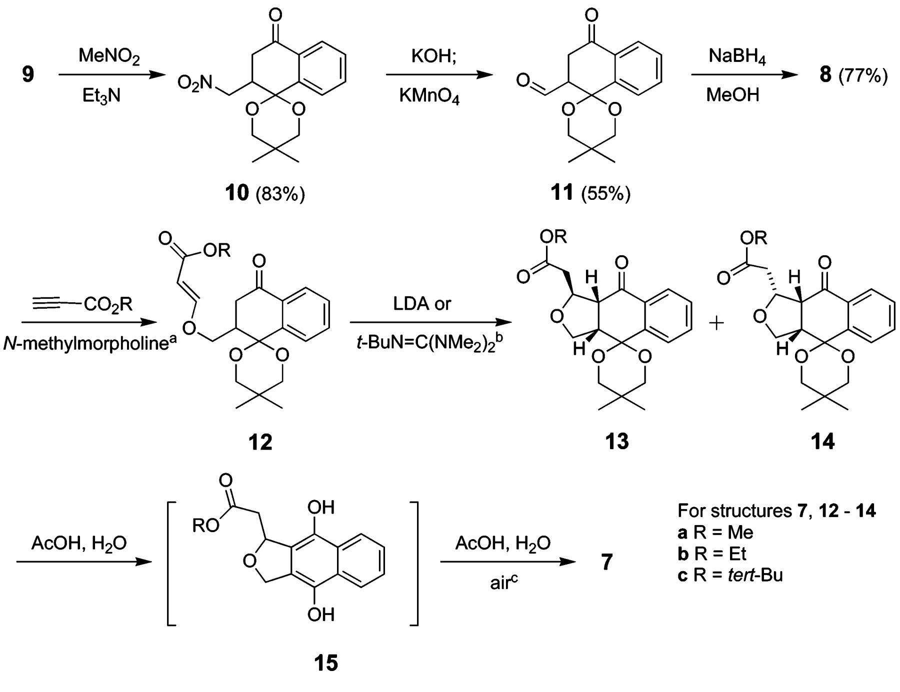
up these initial studies with the total synthesis of the aglycon, (±)-lactonamycinone (**3**).[5] Deville and Behar have published a route to the CDEF ring system[6] as have Kelly and co-workers,[7] and more recently, the Kelly group has described a model asymmetric synthesis of the AB ring system.[8] Retrosynthetically, we considered that the model ABCD ring system (**4**) should be available using a sequence of Michael addition reactions (Scheme 1). In this analysis, the tetracycle **4** was primarily disconnected by the loss of the angular methoxy group (or its equivalent) to reveal butenolide **5**. Butenolide **5** could be derived from the lactone **6** through direct oxidation with IBX or an equivalent transformation.[9] In turn, lactone **6** should be available through oxidative lactonization of naphthoquinone **7** using a dihydroxylation or an epoxidation reaction. Quinone **7** could be disconnected to give alcohol **8** and a propynoate ester. The forward sequence from alcohol **8** to dihydrofuran **7** would involve a double Michael addition reaction to form the B ring and subsequent deprotection and aerobic oxidation. Finally, alcohol **8** should be available from quinone monoketal **9**[10] via the Michael addition of a methanol dianion equivalent.

Results and Discussion

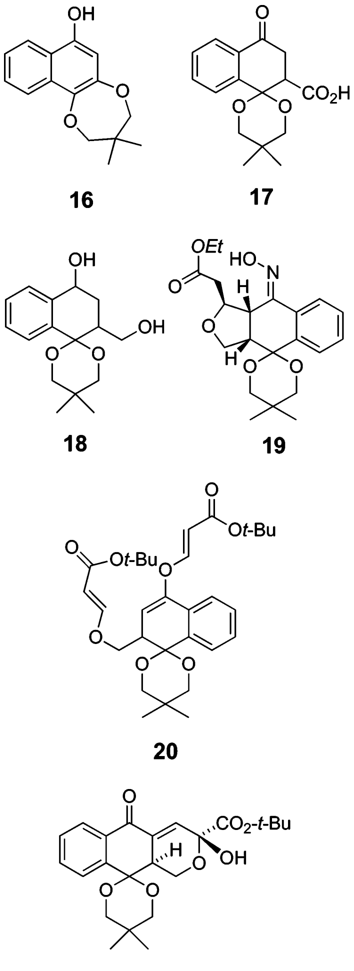
Synthesis of Quinone 7. Quinone monoketal **9** was synthesized in multigram quantities from 4-methoxy-1-naphthol in a modification of the Corey procedure[11] using $PhI(OCOCF_3)_2$-mediated oxidation of 4-methoxy-1-naphthol and 2,2-dimethyl-1,3-propanediol. Since literature precedent indicated that the Michael addition of cuprate reagents to quinone monoketals could be problematic,[12] the copper-mediated addition of a suitably protected hydromethyl organometallic reagent was not examined. Instead, nitromethane was employed as an equivalent reagent. Thus, quinone monoketal **9** was converted into nitroalkane **10** (83%) by the Michael addition of nitromethane nitronate in a process catalyzed by triethylamine. Subsequent oxidative Nef reaction using potassium hydroxide and potassium permanganate in aqueous methanol[13] gave aldehyde **11**, which was reduced to alcohol **8** using sodium borohydride (Scheme 2). Three reactions in this sequence required care in execution to prevent formation of the phenol **16**, an acid-mediated rearrangement product derived from ketal **9**, carboxylic acid **17**, an overoxidation product in the Nef reaction, and diol **18** during formation of alcohol **8** (Figure 2).

Michael addition of alcohol **8** to methyl, ethyl, and *tert*-butyl propynoate, catalyzed by *N*-methylmorpholine, successfully furnished the vinyl ethers **12a**−**c** (68−88%) all as single geometric isomers. Early studies to close the B ring via enolate formation and an intramolecular Michael addition were conducted using lithium diisopropylamide (LDA) as a base and

SCHEME 2. Synthesis of Quinone 7[a]



[a] Key: (a) R = Me (88%), Et (74%), *t*-Bu (68%); (b) LDA: R = Me (41%), Et (45%), *t*-Bu (28%) or *N*-*tert*-butyl-*N*,*N*,*N*,*N*-tetramethylguanidine: R = *t*-Bu (96%); (f) R = Me (70%), *t*-Bu (57%).



16 17 18 19 20 21

FIGURE 2. Structures of minor side products formed in Scheme 2 and oxime **19**.

gave the corresponding tetrahydrofuran acetate esters **13a**−**c** albeit in poor yields (28−45%). In marked contrast, cyclization of the *tert*-butyl ester **12c** using the Barton base *N*-*tert*-butyl-*N*,*N*,*N*,*N*-tetramethylguanidine[14] proceeded in excellent yield (96%) to provide both diastereoisomers **13c** and **14c** (4:6). Treatment of ketal **13a** with aqueous acetic acid (3:7) at 60 °C in the presence of air gave naphthoquinone **7a** (70%). In the same way, reaction of a mixture of **13c** and **14c** gave the quinone **7c** (57%) (Scheme 2). The constitution and stereochemistry of the key intermediates **13** and **14** were confirmed by an X-ray crystallographic structure determination of the oxime **19**[15] derived from ketone **13b** (Figure 2). Again, it is germane to comment on the isolation of side products (Figure 2). The synthesis of enoate **12** was occasionally accompanied by the formation of the double adduct **20** (12%). In addition, a sample of the mixture of ketals **13c** and **14c** underwent oxidative rearrangement on standing for several months to provide the hydroxy ester **21**, the structure of which was established by X-ray crystallography.[15]

Construction of the A Ring. With quinone **7c** in hand, the synthesis of the A ring was investigated. Following the Danishefsky precedent,[4,5] dihydroxylation of **7c** using catalytic quantities of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide gave a mixture of diols **22** and **23** (dr = 7:3) in 70% yield. Separation of the diols was partially achieved by chromatography and recrystallization to give pure **22**, but isolation of the pure minor diastereoisomer **23** was not possible. Thus, the crude mixture of diols **22** and **23** was allowed to stand with excess trifluoroacetic acid in dichloromethane to give lactone **6** in 27% yield (Scheme 3). Presumably, only the minor epimer **23** was able to undergo γ-lactonization. The major isomer **22**, contrary to wishful thinking, did not undergo epimerization to **23** by a possible opening and reclosing of the B ring through a retro-Michael Michael addition process and reclosure. The mass balance of the reaction contained a highly polar product, which was in all probability the corresponding dihydroxy acid of **22**.

The diastereoselectivity of the key dihydroxylation reaction to provide diols **22** and **23** could not be improved in favor of **23** and therefore an alternative method of oxidizing quinone **7c** was investigated. Epoxidation using hydrogen peroxide and sodium carbonate gave a mixture of epoxides **24** and **25** (dr = 6.3:3.7) in 93% yield. The structure and relative stereochemistry of the major diastereoisomer **24** was confirmed by X-ray crystallography.[15] Treatment of **24** with trifluoroacetic acid in dichloromethane led to γ-lactone **26a** (97%), the epimer of lactone **6**. Treatment of epoxide **25** under identical acidic conditions gave the epoxy acid **27** (Scheme 3). Attempted epimerization of **26a** to **6** under acidic or basic conditions resulted in the recovery of starting material **26a** or the formation of intractable mixtures of polar products. Nevertheless, **26a** and subsequently trimethylsilyl ether **26b** were obtained in reasonable quantities and were used as model substrates to investigate the introduction of the angular methoxy group. These studies should be relevant to the possible methoxylation of epimer **6**. The long-term strategy with intermediates such as **26a** may require the use of a nontraditional glycosidation reaction to introduce the α-L-rhodinopyranosyl residue with inversion of stereochemistry.[16] Prior to carrying out such studies, the ketone **26a** was converted into the crystalline oxime **28** and the silyl oxime mesylate **29**. The structure

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(4) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493. Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899.

(5) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5625. Siu, T.; Cox, C. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5629.

(6) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403.

(7) Kelly, T. R.; Xu, D.; Martinez, G.; Wang, H. *Org. Lett.* **2002**, *4*, 1527.

(8) Kelly, T. R.; Xiaolu, C.; Tu, B.; Elliott, E. L.; Grossmann, G.; Laurent, P. *Org. Lett.* **2004**, *6*, 4953.

(9) For examples of the synthesis of unsaturated carbonyl compounds by oxidation using IBX, see: Nicolaou, K. C.; Montagon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993. Nicolaou, K. C.; Gray, D. L. F.; Montagon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

(10) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559.

(11) Sudini, R. R.; Khire, U. R.; Pandey, R. K.; Kumar, P. *Ind. J. Chem. Sect. B.* **2000**, *39*, 738.

(12) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*, 5566.

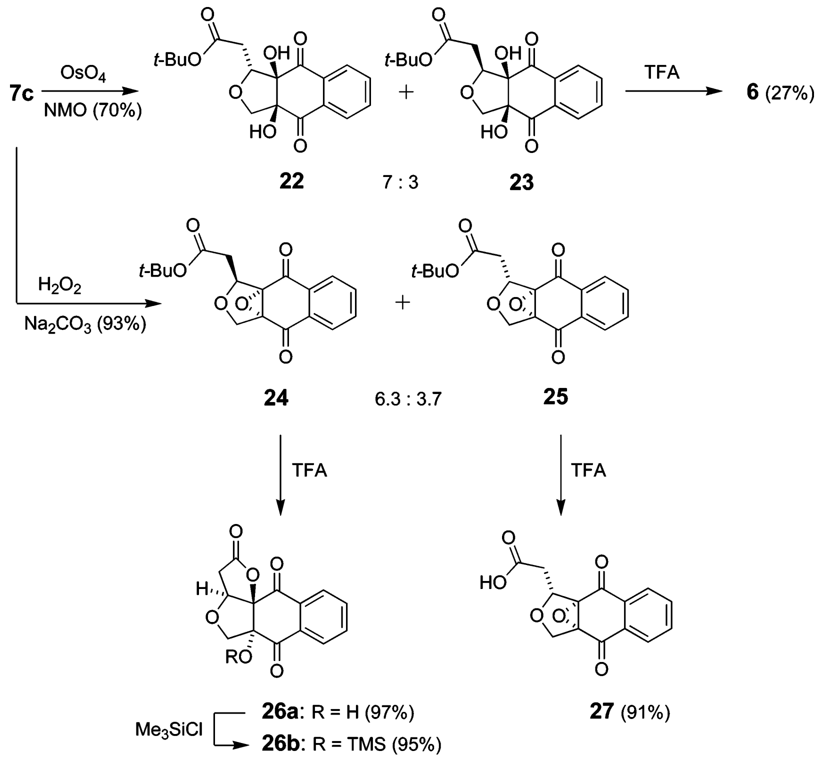
(13) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E., II.; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616.

(14) Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085.

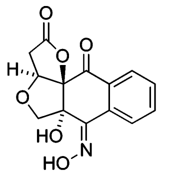
(15) See the Supporting Information for details of the X-ray crystal structure.

(16) It was hoped that unconventional glycosidation methodology, a Michael addition of the anomeric metal alkoxide of a L-rhodinose sugar unit to a transient nitroso-alkene derived from **4**, may be used. See: Barrett, A. G. M.; Trewartha, G. *Tetrahedron Lett.* **2005**, *46*, 3553.

SCHEME 3. Dihydroxylation and Epoxidation of 7



of oxime **28** was confirmed by an X-ray crystallographic study.[15]



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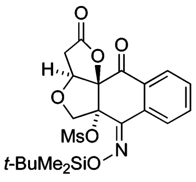

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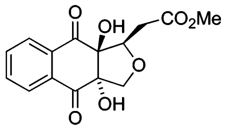

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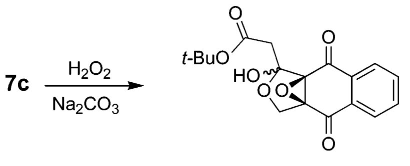
Attempted oxidations of γ-lactones **26a** or **26b** using either IBX-NMO or IBX-MPO[17] to produce the corresponding butenolide, in order to introduce the angular methoxyl group, were unsuccessful. Attempted oxidations with Fenton's reagent,[18] ruthenium chloride and sodium periodate, iodosobenzene diacetate,[19] lead tetracetate and iodine, chromium trioxide and tetrabutyl periodate,[20] ozone and silica,[21] or dimethyldioxirane (DMDO) oxidation[22] were all unsuccessful. For example, attempted Fenton oxidation of the lactone **26a** gave the diol ester **30** (74%). All other attempted oxidations either resulted in starting material being recovered or in the formation of intractable mixtures of products. As a consequence of these failings, we sought to examine introduction of the angular methoxy group at an earlier stage. Oxidation of ester **7c** using hydrogen peroxide and sodium carbonate gave epoxide **31** (Scheme 4). Unfortunately, attempted lactonization of this rather sensitive compound **31** under acidic conditions (TFA$-$CH$_2$Cl$_2$ or camphorsulfonic acid$-$MeOH) gave only intractable mixtures of polar products.

SCHEME 4. Synthesis of Epoxide 31



Synthesis of Carboxylic Acid 33: Masking the Methoxy Group. In light of the difficulties in the attempted oxidations of **26** and **7c**, we considered that it should be possible to mask the methoxy group as a carboxylic acid (see **33**). In this design, the methoxy group would be revealed via late halodecarboxylation,[23] decarboxylative acetoxylation,[24] or through the intermediacy of a methyl perester. In consequence, the retrosynthetic disconnections were slightly modified as in Scheme 5 with the use of di-*tert*-butyl acetylenedicarboxylate as the initial Michael acceptor for reaction with alcohol **8**.

Michael addition of alcohol **8** to di-*tert*-butylacetylene dicarboxylate was optimally catalyzed using 4-(dimethylamino)-pyridine to provide adduct **35** (86%). Cyclization, via a second Michael addition reaction using the Barton base, gave both

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(17) IBX was prepared according to the method of: Frigerio, M.; Santagostino, S.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(18) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125.

(19) Francisco, C. G.; Herrera, A. J.; Suarez, E. *J. Org. Chem.* **2002**, *67*, 7439.

(20) Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978.

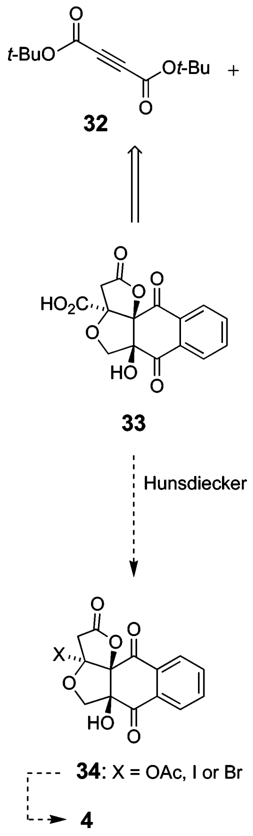
(21) Keinan, E.; Mazur, Y. *Synthesis* **1976**, 524.

(22) Bovicelli, P.; Lupattelli, P.; Fracassi, D. *Tetrahedron Lett.* **1994**, *35*, 935. Yu, B.; Liao, J.; Zhang, J.; Hui, Y. *Tetrahedron Lett.* **2001**, *42*, 77.

(23) Bolster, M. G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2001**, *57*, 5657. Camps, P.; Lukach, A. E.; Pujol, X.; Vazquez, S. *Tetrahedron* **2000**, *56*, 2703. Roy, S. C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 9253.

(24) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279. Thominiaux, C.; Chiaroni, A.; Desmaele, D. *Tetrahedron Lett.* **2002**, *43*, 4107.

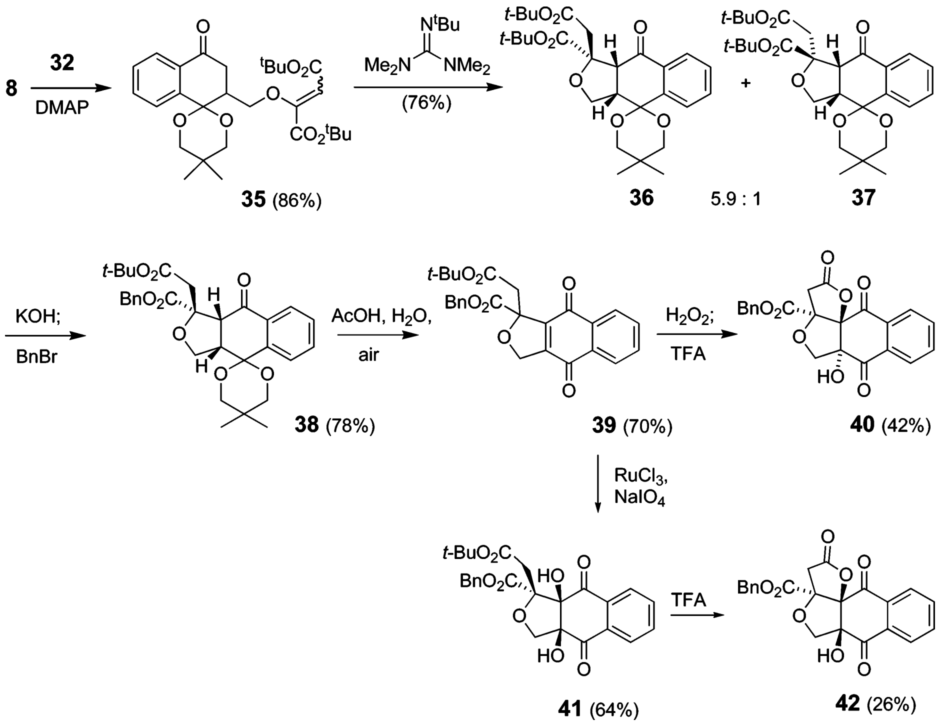
SCHEME 5. Proposed Disconnection of Acid 33 and Its Conversion to the Western Entity 4



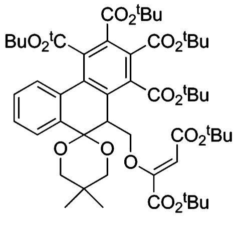
tetrahydrofurans **36** (65%) and **37** (11%). Much to our delight, the diester **36** underwent highly selective monosaponification using potassium hydroxide (vide infra). Subsequent benzylation of the potassium carboxylate using benzyl bromide gave diester **38** (78%). Hydrolysis of ketal **38** by treatment with TFA under aerobic conditions provided quinone **39** (70%). Subsequent epoxidation under basic conditions led to an inseparable 1:1 mixture of diastereoisomeric epoxides, which were directly cyclized using TFA to give *trans*-lactone **40** (42% from **39**) (Scheme 6). Although the quinone **39** failed to react with osmium tetraoxide in stoichiometric quantities, ruthenium(III) chloride catalyzed dihydroxylation[25] of quinone **39** gave diol **41**. Finally, addition of trifluoroacetic acid in dichloromethane gave *cis*-lactone **42** (26%). Again, it is germane to comment on the isolation of side products in this sequence. The synthesis of enoate **35** was accompanied by the formation of the dihydrophenanthrene **43** (8%), the constitution of which was established by spectroscopic data and an X-ray crystallographic structure determination.[15] As an alternative to transesterification, the ketals **36** and **37** were hydrolyzed using 70% aqueous acetic acid in air to give the quinone **44** (52%) and this was further hydrolyzed in trifluoroacetic acid to provide a polar compound tentatively assigned as the diacid **45** (91%).

The selective diester **37** monohydrolysis, carboxylate alkylation, and ketal hydrolysis−oxidation were generalized with the preparation of acid **47**, diesters **46** and **48**, and quinone **49**. At this stage, we had not unequivocally established the regioselectivity of the initial monosaponification of the diester **36**. In fact, we had naively assumed that the less hindered CH$_2$-CO$_2$-*t*-Bu unit would undergo saponification faster. Indeed, TFA-mediated hydrolysis of quinone **49** gave the corresponding carboxylic acid **50**, and this was directly converted into iodide **51** (35% unoptimized). Both the ^{1}H and ^{13}C NMR spectra of this compound were consistent with the presence of an iodomethyl substituent rather than a tertiary iodide. This confirmed that the saponification of diester **36** took place selectively at the more hindered ester. This was confirmed by an X-ray crystal structure of diester **38**.[15] Presumably, the origin of the highly selective saponification of diester **36** was the result of 1,2-

SCHEME 6. Synthesis of Model Aglycons 40 and 42 Using a Carboxylate as a Masked Methoxy Group



hydroxide addition to the ketone and the intermediacy of the lactone alkoxide **52**.



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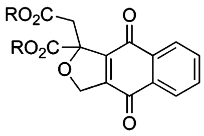
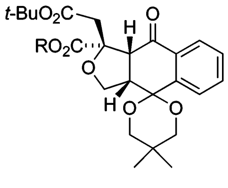
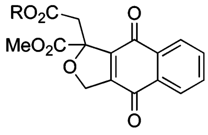


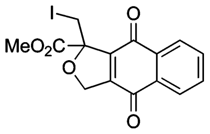
44 R = *t*-Bu
45 R = H



46 R = SEM
47 R = H
48 R = Me



49 R = ${}^tBu$
50 R = H



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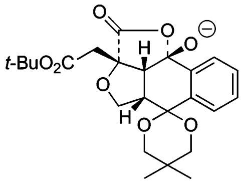

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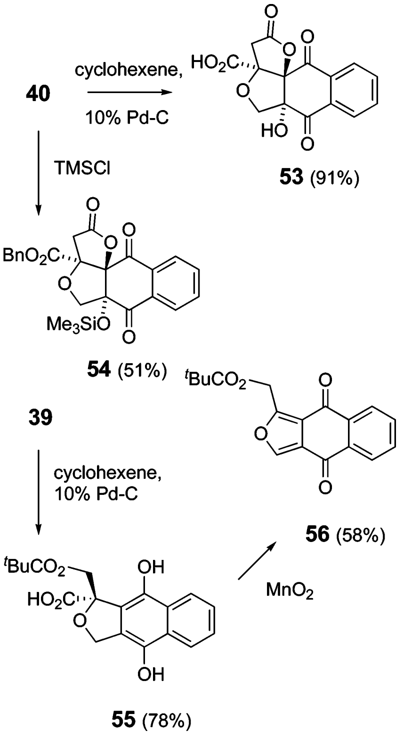
Smooth conversion of ester **40** into carboxylic acid **53** (91%) was achieved by transfer hydrogenation. Alternatively, trimethylsilylation of alcohol **40** gave the silyl ether **54** (51%) (Scheme 7). Selective debenzylation at an earlier stage in the synthetic sequence was briefly explored. Thus, hydrogenolysis of benzyl ester **39** occurred with concomitant quinone reduction giving hydroquinone **55**. Attempted reoxidation of hydroquinone **55** to the quinone oxidation level using excess manganese dioxide was accompanied by oxidative decarboxylation giving the furan **56**.

SCHEME 7. Studies on Debenzylation Reactions



Conclusion

The use of iterative Michael additions and quinone dihydroxylation or epoxidation reactions has been shown to be useful for the concise synthesis of model ring ABCD units of lactonamycin (**1**). Of particular note are the double Michael addition reactions of alcohol **8** to propynoate and acetylenedicarboxylate esters to produce the lactonamycin BCD ring systems **13**, **14**, **36**, and **37**. In addition, the use of the Barton base (*N*-*tert*-butyl-*N*′,*N*′,*N*″,*N*″-tetramethylguanidine) for the intramolecular Michael addition of ketone enolates to β-alkoxyacrylates should be of general synthetic importance.

Experimental Section

4,4-(2,2-Dimethyl-1,3-propylenedioxy)naphthalen-1(4*H*)-one (9). (1) 4-Methoxy-1-naphthol (25.0 g, 144.0 mmol) in CH_2Cl_2 (350 mL) and THF (25 mL) was added dropwise with stirring over 45 min to 2,2-dimethyl-1,3-propanediol (85.0 g, 720 mmol) and $PhI(O_2CCF_3)_2$ (79.9 g, 173.0 mmol) in CH_2Cl_2 (600 mL) at 0 °C. Stirring was continued for a further 45 min, and the mixture allowed to warm to ambient temperature. Saturated aqueous Na_2CO_3 (500 mL) was slowly added over 20 min when precipitation occurred. The solid was filtered off and the filtrate rotary evaporated to ca. half its total volume, washed with saturated aqueous Na_2CO_3 (500 mL), H_2O (250 mL), brine (250 mL), dried ($MgSO_4$), and rotary evaporated. Recrystallization (4:1 hexanes/EtOAc) and drying in vacuo at 50 °C gave enone **9** (14.9 g, 43%) as off-white crystals: mp 139−141 °C (EtOAc/hexanes) (lit.[10] mp 138−142 °C); R_f 0.46 (1:1 hexanes/EtOAc); IR (film) 1672, 1620, 1600, 1470, 1329 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 3H), 1.52 (s, 3H), 3.65 (d, $J = 11.0$ Hz, 2H), 4.06 (d, $J = 11.0$ Hz, 2H), 6.47 (d, $J = 11$ Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.80 (d, $J = 11$ Hz, 1H), 8.01 (d, $J = 7.5$ Hz, 1H), 8.07 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 23.6, 30.1, 71.9, 90.5, 126.0, 126.9, 129.3, 129.4, 129.8, 133.6, 137.3, 142.2, 183.8; MS (CI, NH_3) *m/z* 245 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{15}H_{17}O_3$ $(M + H)^+$ 245.1177, found $(M + H)^+$ 245.1174. (2) 4-Methoxy-1-naphthol (25.8 g, 148 mmol) in dry CH_2Cl_2 (450 mL) was added with stirring over 20 min at 0 °C to 2,2-dimethyl-1,3-propanediol (80.0 g, 768 mmol) and $PhI(O_2CCF_3)_2$ (82.8 g, 224 mmol) in dry CH_2Cl_2 (800 mL) under N_2. After 10 min at 0 °C and a further 45 min at room temperature, saturated aqueous Na_2CO_3 (300 mL) was carefully added. The excess diol precipitated and was filtered and washed with CH_2Cl_2 (300 mL). The organic phase from the mother liquors was separated and the aqueous phase re-extracted with CH_2Cl_2 (150 mL). The combined organic solutions were washed with brine (300 mL), dried ($MgSO_4$), filtered, and rotary evaporated. Recrystallization twice (1:1 cyclohexene/EtOAc) gave spiroketal **9** (23.9 g, 66%) as a white amorphous solid. In this experiment, further recrystallization of the mother liquor gave phenol **16** (8.32 g, 23%) as an off-white solid: mp 207 °C (1:1 cyclohexane/EtOAc); R_f 0.30 (5:1 cyclohexane/EtOAc); IR (film) 3369, 1734, 1664, 1601, 1470, 1396 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.52 (s, 3H), 3.68 (d, $J = 12.0$ Hz, 2H), 4.15 (d, $J = 12.0$ Hz, 2H), 7.53 (td, $J = 1.0, 8.0$ Hz, 1H), 7.71 (td, $J = 1.5, 8.0$ Hz, 1H), 7.95 (s, 1H), 8.04 (dd, $J = 1.0, 8.0$ Hz, 1H),

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[25] Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116.

8.11 (dd, J = 1.5, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.6, 30.2, 71.9, 90.3, 126.7 (2C), 129.4, 129.8, 132.8, 133.8, 138.0, 138.1, 144.8, 182.2; MS (CI, NH_3) m/z 245 (M + H)$^+$; HRMS (CI) m/z calcd for $C_{15}H_{17}O_3$ (M + H)$^+$ 245.1178, found (M + H)$^+$ 245.1177.

(3*RS*)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-nitromethyl-2,3-dihydronaphthalen-1(2*H*)-one (10). $MeNO_2$ (23.0 mL, 418.6 mmol) followed by Et_3N (8.74 mL, 62.8 mmol) were added with stirring to enone **9** (14.6 g, 59.8 mmol) in MeOH (45 mL). After 12 h, the product crystallized directly from the reaction mixture and was filtered off, air-dried, and recrystallized from MeOH to give nitroalkane **10** (15.3 g, 83%) as off-white crystals: mp 146−147 °C (MeOH); R_f 0.5 (1:1 hexanes/EtOAc); IR (film) 1693, 1599, 1532, 1470, 1347, 1285, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.28 (s, 3H), 2.74 (dd, J = 2.5, 18.0 Hz, 1H), 3.08 (dd, J = 4.5, 18.0 Hz, 1H), 3.61 (app-t, J = 11.5 Hz, 2H), 3.81 (app-t, J = 11.5 Hz, 2H), 4.08 (app-br s, 1H), 4.11 (app-t, J = 9.0 Hz, 1H), 4.51 (d, J = 9.0 Hz, 1H), 7.52 (td, J = 1.0, 7.5 Hz, 1H), 7.68 (td, J = 1.0, 7.5 Hz, 1H), 7.88 (dd, J = 1.0, 7.5 Hz, 1H), 8.01 (dd, J = 1.0, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 23.1, 30.1, 34.6, 37.6, 70.6, 71.6, 75.9, 95.7, 125.7, 127.1, 129.8, 131.1, 134.5, 140.7, 194.3; MS (CI, NH_3) m/z 323 (M + NH_4)$^+$ 306 (M + H)$^+$; HRMS (CI) m/z calcd for $C_{16}H_{20}NO_5$ (M + H)$^+$ 306.1341, found (M + H)$^+$ 306.1342. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.16; N, 4.67.

(3*RS*)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-(oxomethyl)-2,3-dihydronaphthalen-1(2*H*)-one (11). (1) KOH in MeOH (1 M; 55.10 mL, 55.1 mmol) was added dropwise over 15 min to nitroalkane **10** (15.20 g, 50.1 mmol) in MeOH (325 mL) at 0 °C. The resulting mixture was stirred for 15 min, and $KMnO_4$ (8.71 g, 55.1 mmol) and $MgSO_4$ (5.41 g, 45.10 mmol) in H_2O (425 mL) were added dropwise over 15 min. The mixture was allowed to warm to ambient temperature over 1 h and quenched by filtration though Celite eluting with Et_2O (100 mL). The filtrate was rotary evaporated, and the resulting aqueous residue was extracted with a mixture of Et_2O and EtOAc (1:1; 3 × 250 mL). The organic extracts were combined, dried ($MgSO_4$), and rotary evaporated. The resultant yellow solid was recrystallized (EtOAc/hexanes) to give two batches of aldehyde **11** (7.56 g, 55%) as fine white needles: mp 143−145 °C (EtOAc/hexanes); R_f 0.32 (1:1 EtOAc/hexanes); IR (film) 1713, 1694, 1598, 1470, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.36 (s, 3H), 2.84 (dd, J = 5.0, 18.0 Hz, 1H), 3.06 (dd, J = 2.5, 18.0 Hz, 1H), 3.60 (dd, J = 2.5, 11.5 Hz, 1H), 3.79−3.82 (m, 2H), 4.09 (d, J = 11.5 Hz, 1H), 4.19 (dd, J = 2.0, 5.0 Hz, 1H), 7.49 (td, J = 1.0, 7.5 Hz, 1H), 7.65 (td, J = 1.0, 7.5 Hz, 1H), 7.90 (dd, J = 1.0, 7.5 Hz, 1H), 7.98 (dd, J = 1.0, 7.5 Hz, 1H), 9.66 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 23.1, 30.2, 34.5, 46.6, 71.0, 71.7, 95.6, 125.2, 126.9, 129.8, 131.2, 134.2, 140.6, 194.4, 200.3; MS (CI, NH_3) m/z 292 (M + NH_4)$^+$ 275 (M + H)$^+$; HRMS (CI) m/z calcd for $C_{16}H_{19}O_4$ (M + H)$^+$ 275.1283, found (M + H)$^+$ 275.1277. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.92; H, 6.57. (2) KOH in MeOH (0.1 M; 271 mL, 27.1 mmol) was added dropwise over 20 min to nitroalkane **10** (7.42 g, 24.6 mmol) in MeOH (174 mL) at 0 °C. $KMnO_4$ (3.89 g, 24.63 mmol) and $MgSO_4$ (2.37 g, 19.7 mmol) in H_2O (454 mL) were added dropwise over 20 min. The mixture was allowed to warm to room temperature over 45 min, filtered through Celite, washed with Et_2O (200 mL) and the filtrate rotary evaporated. The residue was dissolved in EtOAc (300 mL), filtered, and concentrated by rotary evaporation. The crystalline aldehyde **11** (3.81 g) was filtered off, the mother liquor rotary evaporated, and the residue chromatographed (2:1 to 1:2 cyclohexane/EtOAc) to give additional aldehyde **11** (total yield: 4.61 g, 68%, 77% based on recovered nitroalkane **10**) as a white amorphous solid. Further chromatography gave carboxylic acid **17** (712 mg, 10%) as a white amorphous solid: mp 153 °C (EtOAc); R_f 0.25 (EtOAc); IR (film) 3276 (br), 1730, 1695, 1599, 1556 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 0.88 (s, 3H), 1.35 (s, 3H), 2.78−2.92 (m, 2H), 3.50 (d, J = 10.0 Hz, 1H), 3.65 (d, J = 10.0, 1H), 3.97 (d, J = 11.5 Hz, 1H), 4.29 (d, J = 11.5, 1H), 4.48−4.50 (m, 1H), 7.71 (td, J = 1.5, 8.0 Hz, 1H), 7.48−7.52 (m, 1H), 7.65−7.69 (m, 1H), 7.87−7.92 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 20.9, 22.3, 29.3, 37.1, 70.6, 71.1, 95.8, 125.0, 125.5, 126.6, 128.7, 131.9, 133.5, 173.3, 196.5; MS (CI, NH_3) m/z 308 (M + NH_4)$^+$, 292 (M + NH_4 − H_2O)$^+$; HRMS (CI) m/z calcd for $C_{16}H_{22}NO_5$ (M + NH_4)$^+$ 308.1498, found (M + NH_4)$^+$ 308.1501.

(3*RS*)-4,4-(2,2-Dimethyl-1,3-propylenedioxy)-3-hydroxymethyl-2,3-dihydronaphthalen-1(2*H*)-one (8). (1) Sodium borohydride (0.97 g, 25.5 mmol) was added in small portions, over 15 min, to aldehyde **11** (6.36 g, 23.2 mmol) in MeOH (360 mL) at −5 °C. Stirring was continued for a further 30 min, and the reaction was quenched by careful addition of AcOH (5.70 mL). The mixture was rotary evaporated and the resulting residue slurried in EtOAc (150 mL), stirred for 30 min at 40 °C, and filtered though Celite to remove insoluble material. Rotary evaporation and chromatography (1:1 EtOAc/hexanes) gave alcohol **8** (4.94 g, 77%) as a clear oil: R_f 0.18 (1:1 EtOAc/hexanes); IR (film) 3464 (br), 1686, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (s, 3H), 1.30 (s, 3H), 2.19 (br-s, 1H), 2.71 (dd, J = 2.5, 17.5 Hz, 1H), 2.97 (dd, J = 5.0, 17.5 Hz, 1H), 3.44−3.52 (m, 2H), 3.53−3.64 (m, 2H), 3.65−3.71 (m, 1H), 3.84 (d, J = 11.5 Hz, 1H), 3.96 (d, J = 11.5 Hz, 1H), 7.48 (td, J = 1.0, 7.5 Hz, 1H), 7.66 (td, J = 1.0, 7.5 Hz, 1H), 7.92 (dd, J = 1.0, 7.5 Hz, 1H), 7.97 (dd, J = 1.0, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 23.3, 30.1, 36.3, 37.5, 62.9, 70.8, 71.4, 97.4, 125.6, 126.5, 129.3, 131.5, 133.9, 141.4, 196.3; MS (CI, NH_3) m/z 294 (M + NH_4)$^+$, 277 (M + H)$^+$; HRMS (CI) m/z calcd for $C_{16}H_{21}O_4$ (M + H)$^+$ 277.1439, found (M + H)$^+$ 277.1445. (2) $NaBH_4$ (313 mg, 8.28 mmol) was added over 10 min to aldehyde **11** (2.39 g, 8.72 mmol) in dry MeOH (130 mL) at −5 °C under N_2. After 15 min, the reaction was quenched by careful addition of HOAc (2.6 g) and the mixture allowed to warm to room temperature and rotary evaporated. Chromatography (2:1 cyclohexane/EtOAc) gave alcohol **8** (1.48 g, 61%) and subsequently (1:2 cyclohexane/EtOAc) diol **18** (752 mg, 31%): mp 158 °C (EtOAc); R_f 0.31 (EtOAc); IR (film) 3290 (br), 1734, 1716, 1653, 1558, 1508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.26 (s, 3H), 2.05−2.25 (m, 4H), 3.12−3.20 (m, 1H), 3.51−3.61 (m, 4H), 3.79 (d, J = 11.5 Hz, 1H), 3.90 (d, J = 11.5 Hz, 1H), 4.80 (q, J = 8.0 Hz, 1H), 7.39−7.44 (m, 2H), 7.53−7.55 (m, 1H), 7.80−7.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 22.4, 29.2, 29.6, 34.6, 59.1, 64.4, 69.9, 70.6, 97.4, 126.1, 126.3, 126.9, 128.3, 136.8, 139.9; MS (CI, NH_3) m/z 279 (M + H)$^+$, 261 (M + H − H_2O)$^+$; HRMS (CI) m/z calcd for $C_{16}H_{23}O_4$ (M + H)$^+$ 279.1596, found (M + H)$^+$ 279.1600. Activated MnO_2 (1.17 g, 13.5 mmol) was added in four portions over 30 min to diol **18** (752 mg, 2.70 mmol) in CH_2Cl_2 (30 mL) at room temperature. Additional activated MnO_2 (704 mg, 8.10 mmol) was added after 3 h, and the mixture was stirred overnight, filtered through Celite, and rotary evaporated to give alcohol **8** (739 mg, 99%; total yield of alcohol **8** from aldehyde **11** 2.219 g, 91%).

(3*RS*)-*tert*-Butyl 3-((*E*)-(4,4-(2,2-Dimethyl-1,3-propylenedioxy)-2,3-dihydro-1-oxonaphthalen-3-yl)methoxy)acrylate (12c). *tert*-Butyl propynoate (3.20 mL, 23.3 mmol) was added with stirring to *N*-methylmorpholine (2.36 mL, 21.5 mmol) in Et_2O (10 mL). After 30 min, alcohol **8** (4.94 g, 17.9 mmol) in Et_2O (12 mL) was added and stirring continued for 12 h. The mixture was diluted with Et_2O (100 mL) and H_2O (100 mL), shaken vigorously, and the layers were allowed to separate. The aqueous layer was extracted with Et_2O (100 mL), and the organic layers were combined and washed with brine (100 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (1:4 EtOAc/hexanes) gave the double adduct **20** (370 mg, 12%) as a clear oil: R_f 0.73 (1:3 EtOAc/hexanes); IR (film) 2976, 2931, 2871, 1711, 1642, 1624, 1367, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 1.24 (s, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 3.40−3.88 (m, 7H), 4.98 (d, J = 12.5 Hz, 1H), 5.51 (d, 1H, J = 7.0 Hz), 5.57 (d, 1H, J = 12.0 Hz), 7.40 (d, 1H, J = 12.5 Hz), 7.37−7.45 (m, 3H), 7.62 (d, 1H, J = 12.0 Hz), 7.76−7.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 22.5, 23.3, 28.2, 30.54, 70.4, 70.6, 71.2, 76.7, 77.0, 77.4, 79.7, 80.2, 96.5, 98.4, 104.6, 105.3, 122.3, 125.0, 128.7, 129.1, 129.3, 135.5, 150.6, 161.3, 166.4, 166.9; MS (CI, NH_3) *m/z* 546 $(M + NH_4)^+$, 529 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{30}H_{40}O_8$ $(M + NH_4)^+$ 529.2801, found $(M + NH_4)^+$ 529.2799. Anal. Calcd for $C_{30}H_{40}O_8$: C, 68.16; H, 7.63. Found: C, 68.25; H 7.70. Further elution gave enoate **12c** (6.37 g, 68%) as a clear oil: R_f 0.32 (1:3 EtOAc/hexanes); IR (film) 1694, 1686, 1642, 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.26 (s, 3H), 1.38 (s, 9H), 2.79 (dd, *J* = 2.5, 18.0 Hz, 1H), 2.90 (dd, *J* = 5.0, 18.0 Hz, 1H), 3.45−3.59 (m, 2H), 3.62−3.67 (m, 2H), 3.82 (app-t, *J* = 10.0 Hz, 2H) 3.89 (dd, *J* = 5.0, 10.0 Hz, 1H), 4.87 (d, *J* = 12.5 Hz, 1H), 7.32 (d, *J* = 12.5 Hz, 1H), 7.41 (t, *J* = 1.0, 7.5 Hz, 1H), 7.61 (t, *J* = 1.0, 7.5 Hz, 1H), 7.82 (td, *J* = 1.0, 7.5 Hz, 1H), 7.91 (td, *J* = 1.0, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 23.3, 28.3, 30.1, 34.1, 36.9, 69.5, 70.5, 71.5, 79.9, 95.9, 98.6, 125.7, 126.6, 129.4, 131.4, 134.4, 141.1, 161.0, 166.8, 195.5; MS (CI, NH_3) *m/z* 403 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{23}H_{31}O_6$ $(M + H)^+$ 403.2121, found $(M + H)^+$ 403.2131.

(1*SR*,3a*SR*,9a*RS*)-*tert*-Butyl 4,4-(2,2-Dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (13c) and (1*RS*,3a*SR*,9a*RS*)-*tert*-Butyl 4,4-(2,2-Dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (14c). (1) Reaction of acrylate **12c** (0.101 g, 0.25 mmol) with LiN(*i*-Pr)$_2$ as for **12a** and chromatography (4:1 hexanes/EtOAc) gave **13c** (30 mg, 28%) as a clear oil. (2) 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (2.5 mL, 12.26 mmol) was added with stirring to acrylate **12c** (4.48 g, 11.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After 10 min, the mixture was stirred at ambient temperature for 8 h, diluted with CH_2Cl_2 (150 mL) and H_2O (100 mL), shaken vigorously, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the organic layers were combined, washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (1:5 EtOAc/hexanes) gave tetrahydrofurans **13c** and **14c** (4.30 g, 96%), a 4:6 mixture of diastereoisomers, as a clear oil: R_f 0.32 (1:3 EtOAc/hexanes); IR (film) 1731, 1685, 1367, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (s, 3H), 1.15 (s, 1.8H), 1.18 (s, 1.2H), 1.48 (s, 9H), 2.33 (dd, *J* = 8.0, 17.0 Hz, 0.6H), 2.59−2.78 (m, 1.4H), 3.07 (dd, *J* = 4.5, 9.0 Hz, 0.4H), 3.28 (app-t, *J* = 5.5 Hz, 0.6H), 3.30−4.95 (m, 6H), 4.05−4.20 (m, 1H), 4.33 (dt, *J* = 4.5, 8.0 Hz, 0.4H), 4.41 (dt, *J* = 5.5, 8.0 Hz, 0.6H), 7.50 (app-q, *J* = 7.5 Hz, 1H), 7.59−7.69 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 0.4H), 7.87 (m, 1.6H); ^{13}C NMR ($CDCl_3$, 75 MHz) both isomers δ 22.5, 23.1, 28.1, 30.2, 37.3, 39.7, 40.2, 41.4, 51.4, 52.9, 68.1, 69.2, 71.0, 71.1, 71.3, 79.4, 80.4, 80.9, 81.0, 95.5, 96.3, 125.3, 125.4, 126.2, 127.3, 129.3, 132.2, 133.2, 134.3, 141.1, 141.4, 169.8, 170.3, 197.0, 197.4; MS (CI, NH_3) *m/z* 403 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{23}H_{31}O_6$ $(M + H)^+$ 403.2121, found $(M + H)^+$ 403.2116. A sample of the crude mixed esters **13c** and **14c** was found to deposit crystals on standing at room temperature over several months. These were assigned as hydroxy ester **21** by an X-ray crystallographic study.[15]

(1*SR*)-*tert*-Butyl (4,9-Dioxo-1,3,4,9-tetrahydronaphtho[2,3-*c*]-furan-1-yl)acetate (7c). (1) AcOH in H_2O (7:3; 20 mL) was added to ketals **13c** and **14c** (3.61 g, 8.98 mmol) and the mixture heated at 60 °C under an atmosphere of air for 12 h. After being cooled to ambient temperature, the orange solution was rotary evaporated, the residue was partitioned between H_2O (150 mL) and Et_2O (150 mL), shaken vigorously, and the layers were allowed to separate. The aqueous layer was extracted with Et_2O (2 × 100 mL), the organic layers combined, washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (1:9 EtOAc/hexanes) gave quinone **7c** (1.61 g, 57%) as an orange oil that slowly solidified upon standing: R_f 0.4 (1:3 EtOAc/hexanes); IR (film) 1731, 1667, 1621, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (s, 9H), 2.80 (dd, *J* = 6.5, 16.0 Hz, 1H), 3.04 (dd, *J* = 4.0, 16.0 Hz, 1H), 5.06 (dd, *J* = 4.5, 16.0 Hz, 1H), 5.14 (dd, *J* = 6.0, 16.0 Hz, 1H), 5.65 (m, 1H), 7.74−7.78 (m, 2H), 8.08−8.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 40.2, 72.6, 81.1, 82.0, 126.4, 126.5, 132.8, 132.9, 133.9, 134.0, 146.6, 146.7, 169.3, 181.4, 181.6; MS (CI, NH_3) *m/z* 315 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{19}O_5$ $(M + H)^+$ 315.1232, found $(M + H)^+$ 315.1218. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.82; H, 5.86. (2) TsOH•H_2O (72 mg, 0.379 mmol) was added with stirring to ketals **13c** and **14c** (102 mg, 0.253 mmol) in Me_2CO (10 mL). After the mixture was stirred overnight, saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (3:1 cyclohexane/EtOAc) to give quinone **7c** (61 mg, 77%) as a yellow solid.

(1*RS*,3a*SR*,9a*RS*)-*tert*-Butyl (3a,9a-Dihydroxy-4,9-dioxo-1,3,-3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (22) and (1*SR*,3a*SR*,9a*RS*)-*tert*-Butyl (3a,9a-Dihydroxy-4,9-dioxo-1,3,-3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (23). *N*-Methylmorpholine *N*-oxide (0.66 g, 5.55 mmol) followed by OsO_4 in *t*-BuOH (2.5 wt %; 1.50 mL, 0.25 mmol) were added to quinone **7c** (1.58 g, 5.03 mmol) in Me_2CO and H_2O (1:1; 30 mL) at 0 °C. The mixture was stirred at ambient temperature for 12 h, after which saturated aqueous Na_2SO_3 (10 mL) was added and the mixture stirred for a further 15 min and diluted with H_2O (10 mL). The aqueous portion was extracted with EtOAc (3 × 50 mL), and the organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (2:3 EtOAc/hexanes) to give diols **22** and **23** (1.23 g, 70%), a 7:3 mixture of diastereoisomers, as a white solid. A small sample of the major diastereoisomer **22** (15 mg) was isolated by further chromatography (3:7 EtOAc/hexanes) as a white solid: mp 138−140 °C (CH_2Cl_2); R_f 0.38 (1:1 EtOAc/hexanes); IR (film) 3383 (br), 1723, 1696, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H), 2.63 (dd, *J* = 7.0, 14.5 Hz, 1H), 2.69 (dd, *J* = 7.0, 14.5 Hz, 1H), 3.50 (s, 1H), 3.87 (d, *J* = 9.0 Hz, 1H), 4.53 (d, *J* = 9.0 Hz, 1H), 4.57 (t, *J* = 7.0 Hz, 1H), 4.60 (s, 1H), 7.83−7.88 (m, 2H), 8.08−8.11 (m, 1H), 8.18−8.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 35.7, 72.9, 80.6, 81.6, 84.0, 84.7, 127.7, 128.2, 132.7, 132.8, 135.5, 135.6, 169.8, 192.4, 195.3; MS (CI, NH_3) *m/z* 366 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{24}NO_7$ $(M + NH_4)^+$ 366.1545, found $(M + NH_4)^+$ 366.1553. Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.29: H, 5.60. The data reported for diol **23** refers to a chromatographed white solid containing both **23** and **22** (68:22): R_f 0.37 (1:1 EtOAc/hexanes); IR (film) 3383 (br), 1723, 1696, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 2.51 (dd, *J* = 7.5, 17.0 Hz, 1H), 2.85 (dd, *J* = 6.5, 17.0 Hz, 1H), 4.00 (d, *J* = 10.5 Hz, 1H), 4.15 (br-s, 1H), 4.27 (d, *J* = 10.5 Hz, 1H), 4.43 (dd, *J* = 6.5, 7.5 Hz, 1H), 5.10 (br-s, 1H), 7.82−7.84 (m, 2H), 8.04−8.06 (m, 2H); MS (CI, NH_3) *m/z* 366 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{24}NO_7$ $(M + NH_4)^+$ 366.1545, found $(M + NH_4)^+$ 366.1553. Anal. Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.29; H 5.60.

(3a*SR*,5a*SR*,11a*RS*)-5a-Hydroxy-3,3a,5,5a-tetrahydrofuro[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (6). Diols **22** and **23** (1.51 g, 4.34 mmol) were dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C, and a mixture of TFA and H_2O (9:1; 3 mL) was added. After 10 min at 0 °C and a further 12 h at room temperature, the mixture was rotary evaporated, the residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL), shaken vigorously, and the layers were allowed to separate. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (1:2−1:1 EtOAc/hexanes) and recrystallization from EtOAc/hexanes gave hydroxy ketone **6** (0.321 g, 27%) as a white crystalline solid: mp 174−175 °C (EtOAc/hexanes) (lit.[4] mp 173 °C dec); R_f 0.26 (1:1 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.78 (dd, *J* = 2.0, 19.0 Hz, 1H), 2.92 (dd, *J* = 7.0, 19.0 Hz, 1H), 3.52 (s, 1H), 3.94 (d, *J* = 10.0 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 4.75 (dd, *J* = 2.0, 7.0 Hz, 1H), 7.89−7.94 (m, 2H), 8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9, 75.2, 80.9, 83.6, 91.9, 128.1, 128.3, 132.2, 133.2, 135.8, 136.3, 173.4, 189.2, 191.7; MS (CI, NH_3) *m/z* 292 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{14}H_{14}NO_6$ $(M + NH_4)^+$ 292.0821, found $(M + NH_4)^+$ 292.0815. Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.31; H 3.58.

(1*SR*,3a*RS*,9a*SR*)-*tert*-Butyl (3a,9a-Epoxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (24) and (1*RS*,3a*RS*,9a*SR*)-*tert*-Butyl (3a,9a-Epoxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl)acetate (25). Aqueous H_2O_2 (30 wt %; 13 mL) was added with stirring to quinone **7c** (1.30 g, 4.14 mmol) in THF (45 mL) at ambient temperature. Na_2CO_3 (0.44 g, 4.55 mmol) in H_2O (4.4 mL) was added dropwise over 2 min, with the orange solution quickly turning colorless. Stirring was continued at ambient temperature for 1 h, and the mixture was poured into ice-cold saturated aqueous Na_2SO_3 (150 mL) and stirred vigorously for 30 min. The product was extracted with Et_2O (2 × 100 mL), and the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The crude mixture of epoxides (6.3:3.7, **24**:**25**) was chromatographed (1:5 EtOAc/hexanes) to give epoxide **24** (0.83 g, 60%) as a white solid: mp 116−117 °C ($CHCl_3$); R_f 0.47 (1:3 EtOAc/hexanes); IR (film) 1720, 1698, 1247, 906 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 9H), 2.88 (dd, $J = 4.0$, 16.5 Hz, 1H), 3.15 (dd, $J = 4.0$, 16.5 Hz, 1H), 4.30 (d, $J = 14.0$ Hz, 1H), 4.39 (d, $J = 14.0$ Hz, 1H), 4.75 (t, $J = 4.0$ Hz, 1H), 7.79 (m, 2H), 8.03−8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9, 37.7, 65.9, 68.9, 69.3, 74.2, 81.6, 127.4, 127.6, 132.8, 132.9, 134.6, 134.7, 170.4, 188.4, 189.5; MS (CI, NH_3) *m/z* 348 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{22}NO_6$ $(M + NH_4)^+$ 348.1447, found $(M + NH_4)^+$ 348.1447. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.59; H, 5.61. Further elution gave epoxide **25** (0.46 g, 33%) as a white amorphous solid: R_f 0.38 (1:3 EtOAc/hexanes); IR (film) 1730, 1699, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 9H), 2.66 (dd, $J = 10.0$, 16.0 Hz, 1H), 3.03 (dd, $J = 2.5$, 16.0 Hz, 1H), 4.27 (d, $J = 11.0$ Hz, 1H), 4.43 (d, $J = 11.0$ Hz, 1H), 4.84 (dd, $J = 2.5$, 10.0 Hz, 1H), 7.79−7.82 (m, 2H), 8.02−8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 37.0, 64.9, 67.7 (2-*C*), 72.7, 81.3, 127.4, 127.5, 132.9 (2-*C*), 134.8, 134.9, 169.4, 189.1 (2-*C*); MS (CI, NH_3) *m/z* 348 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{18}H_{22}NO_6$ $(M + NH_4)^+$ 348.1447, found $(M + NH_4)^+$ 348.1447. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.59; H, 5.61.

(3a*SR*,5a*RS*,11a*RS*)-5a-Hydroxy-3,3a,5,5a-tetrahydrofuro[3,2-*b*]naphtho[2,3-*c*]furan-2,6,11-trione (26a). Epoxide **24** (0.53 g, 1.61 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, and TFA (2 mL) was added dropwise with stirring over 2 min. After 0.5 h, the mixture was allowed to warm to room temperature and stirred for a further 3 h. After rotary evaporation, the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the organic layers were combined, washed with brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The crude product was purified by dilution with EtOAc (100 mL) and filtration though a short plug of silica gel (1:1 EtOAc/hexanes) to give a beige solid, which was recrystallized from EtOAc/hexanes to give lactone **26a** (0.43 g, 97%) as a white crystalline solid: mp 192−194 °C (EtOAc/hexanes) (lit.[4] mp 187 °C dec); R_f 0.34 (1:1 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (d, $J = 18.5$ Hz, 1H), 2.99 (dd, $J = 4.5$, 18.5 Hz, 1H), 3.68 (s, 1H), 4.24 (d, $J = 11.0$ Hz, 1H), 4.50 (d, $J = 11.0$ Hz, 1H), 5.34 (d, $J = 4.5$ Hz, 1H), 7.83−7.85 (m, 2H), 8.12−8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 35.9, 72.1, 80.4, 84.1, 92.5, 127.2, 127.4, 128.1, 132.1, 133.5, 135.1, 135.6, 173.8, 189.0, 191.7; MS (CI, NH_3) *m/z* 292 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{14}H_{14}NO_6$ $(M + NH_4)^+$ 292.0821, found $(M + NH_4)^+$ 292.0827. Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.19; H, 3.63.

(3*RS*)-*tert*-Butyl 3-((*E*)-(4,4-(2,2-Dimethyl-1,3-propylenedioxy)-2,3-dihydro-1-oxonaphthalen-3-yl)methoxy)fumarate (35). 4-(Dimethylamino)pyridine (60 mg, 82 μmol) was added with stirring to alcohol **8** (673 mg, 2.44 mmol) and di-*tert*-butyl acetylenedicarboxylate **32** (716 mg, 3.17 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under N_2. After being stirred overnight, the mixture was diluted with brine (40 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (5:1 cyclohexane/EtOAc) to give dihydrophenanthrene **43** (183 mg, 8%) as a white solid: mp 198 °C dec (5:1 hexanes/EtOAc); R_f 0.24 (5:1 hexanes/EtOAc); IR (film) 1722 (br), 1633, 1478, 1459 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.24 (s, 12H), 1.40 (s, 18H), 1.62 (s, 18H), 1.71 (s, 9H), 3.23 (d, $J = 11.5$ Hz, 1H), 3.50−3.58 (m, 2H), 3.65 (t, $J = 8.0$ Hz, 1H), 4.08−4.11 (m, 1H), 4.21 (d, $J = 12.0$ Hz, 1H), 4.38−4.41 (m, 1H), 5.75 (s, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 7.40 (d, $J = 7.5$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.88 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 23.6, 27.7 (2C), 27.9 (2C), 28.2 (2C), 30.0, 39.3, 70.7, 71.8, 72.4, 80.5, 82.6, 83.5, 83.7 (x3), 84.0 (2C), 97.6, 104.6, 125.3, 127.9, 128.4, 129.2, 130.2, 131.4, 131.9, 133.5, 134.1, 134.8, 135.4, 137.1, 153.3, 161.9, 163.8, 165.8, 166.2, 166.6, 167.8, 171.2; MS (FAB) *m/z* 936 $(M^{+\bullet})$; HRMS (FAB) *m/z* calc for $C_{52}H_{72}O_{15}$ $M^{+\bullet}$ 936.4871, found $M^{+\bullet}$ 936.4828. Further elution gave ester **35** (1.06 g, 86%) as a colorless oil: R_f 0.21 (5:1 cyclohexene/EtOAc); IR (film) 1719, 1690, 1476 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.26 (s, 3H), 1.36 (s, 9H), 1.39 (s, 9H), 2.86 (dd, $J = 2.5$, 18.0 Hz, 1H), 3.10 (d, $J = 18.0$ Hz, 1H), 3.43−3.56 (m, 3H), 3.74−3.80 (m, 1H), 3.82 (d, $J = 11.5$ Hz, 1H), 3.97 (d, $J = 11.5$ Hz, 1H), 4.08−4.11 (m, 1H), 5.97 (s, 1H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.92 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.3, 27.8, 28.0, 29.8, 34.6, 36.4, 70.2, 71.4, 72.3, 81.1, 82.9, 95.8, 111.0, 125.5, 126.4, 129.2, 131.5, 134.0, 141.6, 153.8, 161.8, 163.6, 195.8; MS (CI, NH_3) *m/z* 503 $(M + H)^+$, 464 $(M - C_4H_8 + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{28}H_{39}O_8$ $(M + H)^+$ 503.2645, found $(M + H)^+$ 503.2665.

(1*RS*,3a*SR*,9a*RS*)-*tert*-Butyl ((1-*tert*-Butyloxycarbonyl)-4,4-(2,2-dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl))acetate (36) and (1*SR*,3a*SR*,9a*RS*)-Di-*tert*-butyl ((1-*tert*-Butyloxycarbonyl)-4,4-(2,2-dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl))acetate (37). 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (360 mg, 2.10 mmol) was added with stirring to ester **35** (1.056 g, 2.10 mmol) in dry CH_2Cl_2 (15 mL) at room temperature under N_2. After being stirred overnight, the mixture was diluted with brine (40 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (5:1 cyclohexane/EtOAc) to give ester **37** (113 mg, 11%) as a colorless oil: R_f 0.22 (5:1 cyclohexene/EtOAc); IR (film) 1735, 1688, 1458, 1369 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.15 (s, 3H), 1.45 (s, 9H), 1.53 (s, 9H), 2.47 (d, $J = 17.5$ Hz, 1H), 3.00 (d, $J = 17.5$ Hz, 1H), 3.34 (d, $J = 11.5$ Hz, 1H), 3.42 (d, $J = 8.0$ Hz, 1H), 3.58 (t, $J = 8.0$ Hz, 1H), 3.68 (d, $J = 11.5$ Hz, 2H), 3.86 (d, $J = 11.5$ Hz, 1H), 4.11−4.21 (m, 1H), 4.34 (d, $J = 9.0$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.1, 27.9, 28.1, 30.2, 39.1, 40.7, 54.1, 69.8, 71.1, 71.3, 81.1, 82.0, 87.4, 96.0, 125.2, 126.5, 129.4, 133.4, 133.6, 141.0, 169.0, 171.1, 196.3; MS (CI, NH_3) *m/z* 520 $(M + NH_4)^+$, 503 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{28}H_{39}O_8$ $(M + H)^+$ 503.2645, found $(M + H)^+$ 503.2665. Further elution (3:1 cyclohexane/EtOAc) gave diastereoisomeric ester **36** (687 mg, 65%) as a white solid: mp 170 °C (CH_2Cl_2/Et_2O); R_f 0.16 (5:1 cyclohexene/EtOAc); IR (film) 1736, 1687, 1455, 1368 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.19 (s, 3H), 1.34 (s, 9H), 1.47 (s, 9H), 2.81 (d, $J = 15.5$ Hz, 1H), 3.10 (d, $J = 15.5$ Hz, 1H), 3.38 (d, $J = 11.5$ Hz, 1H), 3.53 (d, $J = 8.0$ Hz, 1H), 3.64−3.90 (m, 4H), 3.92−4.10 (m, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.2, 27.7, 28.1, 30.1, 39.0, 43.9, 55.3, 70.6, 71.0, 71.2, 80.9, 82.4, 88.2, 95.0, 124.9, 127.2, 129.3, 132.8, 133.7, 140.8, 169.1, 169.7, 195.3; MS (CI, NH_3) *m/z* 520 $(M + NH_4)^+$, 503 $(M + H)^+$; HRMS (CI) *m/z* calcd for $C_{28}H_{39}O_8$ 503 $(M + H)^+$ 503.2645, found 503 $(M + H)^+$ 503.2656. Anal. Calcd for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 67.05; H, 7.79.

(1*RS*,3a*SR*,9a*RS*)-*tert*-Butyl ((1-Benzyloxycarbonyl)-4,4-(2,2-dimethyl-1,3-propylenedioxy)-9-oxo-(1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-yl))acetate (38). Aqueous KOH (0.384 M; 3 mL, 1.153 mmol) was added with stirring to diester **36** (579 mg, 1.153 mmol) in dioxane (6 mL) at room temperature. After being allowed to stand overnight, the mixture was rotary evaporated and azeotroped with PhMe (20 mL) to give an off-white solid. This was suspended in DMF (10 mL), $PhCH_2Br$ (394 mg, 2.31 mmol) was added, and the mixture was stirred overnight. Et_2O (50 mL) and H_2O (50 mL) were added, the aqueous layer was further extracted with Et_2O (50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, rotary evaporated, and chromatographed (5:1 cyclohexane/EtOAc) to give ester **38** (484 mg, 78%) as a colorless solid: mp 172 °C (2:1 cyclohexane/EtOAc); R_f 0.30 (2:1 cyclohexane/EtOAc); IR (film) 1736, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.17 (s, 3H), 1.42 (s, 9H), 2.83 (d, $J = 15.5$ Hz, 1H), 3.27 (d, $J = 15.5$ Hz, 1H), 3.36 (d, $J = 11.5$ Hz, 1H), 3.49 (d, $J = 7.5$ Hz, 1H), 3.67−3.89 (m, 4H), 4.07−4.15 (m, 2H), 5.02 (d, $J = 12.5$ Hz, 1H), 5.10 (d, $J = 12.5$ Hz, 1H), 7.29 (m, 5H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.57−7.66 (m, 2H), 7.84 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 22.6, 27.4, 29.6, 38.9, 43.3, 55.5, 66.7, 69.3, 71.0 (2C), 80.8, 88.0, 94.7, 124.4, 126.5, 127.6, 127.7, 127.8, 128.8, 132.3, 133.1, 134.7, 140.1, 167.8, 169.8, 195.0; MS (CI, NH_3) *m/z* 554 $(M + NH_4)^+$, 537 $(M + H)^+$, 481; HRMS (CI) *m/z* calcd for $C_{31}H_{37}O_8$ $(M + H)^+$ 537.2488, found $(M + H)^+$ 537.2484. Anal. Calcd for $C_{31}H_{36}O_8$: C, 69.39; H, 6.76. Found: C, 69.45; H, 6.70.

(1*SR*)-*tert*-Butyl (1-(Benzyloxycarbonyl)-4,9-dioxo-1,3,4,9-tetrahydronaphtho[2,3-*c*]furan-1-yl)acetate (39). Diester **38** (2.58 g, 4.81 mmol) was heated to 55 °C in 70% aqueous HOAc (25 mL) for 13 h, rotary evaporated, and chromatographed (8:1 cyclohexane/EtOAc) to give quinone **39** (1.508 g, 70%) as a yellow solid: mp 108 °C (EtOAc); R_f 0.46 (2:1 cyclohexane/EtOAc); IR (film) 1735, 1669, 1594, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 3.33−3.37 (m, 2H), 5.17−5.23 (m, 4H), 7.29−7.32 (m, 5H), 7.74−7.80 (m, 2H), 8.08−8.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 41.1, 68.2, 73.9, 81.7, 91.2, 126.8, 127.1, 128.3, 128.8, 129.0, 133.2 (2C), 134.4, 134.6, 135.4, 145.1, 148.1, 168.6, 169.3, 180.8, 181.9; MS (CI, NH_3) *m/z* 468 $(M + NH_4 + H_2)^+$, 466 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{26}H_{30}NO_7$ $(M + NH_4 + H_2)^+$ 468.2022, found $(M + NH_4 + H_2)^+$ 468.2018. Anal. Calcd for $C_{26}H_{28}O_7$: C, 69.63; H, 5.39. Found: C, 69.80; H, 5.27.

(3a*SR*,5a*RS*,11a*SR*)-Benzyl 5a-Hydroxy-2,6,11-trioxo-3,3a,5,-5a-tetrahydrofuro[3,2-*b*]naphtho[2,3-*c*]furan-3a-carboxylate (40). K_2CO_3 (27 mg, 0.196 mmol) was added with stirring to quinone **39** (88 mg, 0.196 mmol) and 50% aqueous H_2O_2 (133 μL, 1.96 mmol) in THF (3 mL). After overnight stirring, saturated aqueous sodium sulfite (3 mL) and Et_2O (10 mL) were added, and the aqueous phase was extracted with Et_2O (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and rotary evaporated. The crude epoxide(s) was dissolved in CH_2Cl_2 (3 mL), and TFA (0.5 mL) was added. After 4 h, the mixture was rotary evaporated and the residue dissolved in EtOAc, filtered through silica, and rotary evaporated. Half of the product was dissolved in PhMe (4 mL) and TFA (0.3 mL), heated at 110 °C for 3 h, rotary evaporated, and chromatographed (2:1 cyclohexane/EtOAc) to give lactone **40** (17 mg, 42%) as a white solid: mp 155 °C (cyclohexene/EtOAc 5/1); R_f 0.28 (2:1 cyclohexane:EtOAc); IR (film) 3307, 1816, 1720, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (d, $J = 18.5$ Hz, 1H), 3.62 (d, $J = 18.5$ Hz, 1H), 4.55 (d, $J = 10.5$ Hz, 1H), 4.66 (d, $J = 10.5$ Hz, 1H), 5.38 (d, $J = 12.0$ Hz, 1H), 5.44 (d, $J = 12.0$ Hz, 1H), 6.03 (s, 1H), 7.46−7.50 (m, 5H), 7.77−7.88 (m, 2H), 8.10 (d, $J = 7.0$ Hz, 1H), 8.16 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.8, 70.3, 75.4, 84.6, 86.9, 95.0, 127.8, 128.4, 128.9 (3C), 129.3, 133.6, 134.4, 135.3, 135.4, 169.8, 170.1, 187.3, 188.1; MS (CI, NH_3) *m/z* 426 $(M + NH_4)^+$, 340; HRMS (CI) *m/z* calcd for $C_{22}H_{20}O_8N$ $(M + NH_4)^+$ 426.1189, found $(M + NH_4)^+$ 426.1178. Anal. Calcd for $C_{22}H_{16}O_8$: C, 64.71; H, 3.95. Found: C, 64.54; H, 3.81.

Benzyl (1*SR*,3a*SR*,9a*RS*)-1-((*tert*-Butyloxycarbonyl)methyl)-3a,9a-dihydroxy-4,9-dioxo-1,3,3a,4,9,9a-hexahydronaphtho[2,3-*c*]furan-1-carboxylate (41). $RuCl_3$ (2 mg 0.5%), $NaIO_4$ (0.652 g, 3.05 mmol), and H_2SO_4 (0.023 mL, 0.4 mmol) were added to quinone **39** (0.911 g, 2.03 mmol) in EtOAc, CH_3CN, and H_2O (6:6:1, 26 mL) at 0 °C and the mixture stirred for 2 h. The solution was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), the aqueous phase was separated and extracted with EtOAc (3 × 25 mL), and the combined organic extracts were dried ($MgSO_4$). Rotary evaporation and chromatography (7:3 pentane/EtOAc) gave diol **41** as a white solid (0.624 g, 64%): IR (film) 3426, 1732, 1698, 1593, 1455, 1369, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 9H), 1.96 (d, $J = 15.5$ Hz, 1H), 2.80 (d, $J = 15.5$ Hz, 1H), 4.15 (d, $J = 9.0$ Hz, 1H), 4.82 (d, $J = 9.0$ Hz, 1H), 5.30 (s, 2H), 7.29−7.48 (m, 5H), 7.89−7.94 (m, 2H), 8.14−8.18 (m, 1H), 8.25−8.27 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 27.8, 42.1, 67.4, 72.8, 82.2, 82.4, 84.2, 89.9, 127.4, 128.4, 128.5 (3C), 128.7, 133.6, 133.9, 135.7, 136.4, 167.0, 168.7, 191.0, 194.1; MS (Cl, NH_3) *m/z* 500 $(M + NH_4)^+$; HRMS calcd for $C_{26}H_{26}O_9$ $(M + NH_4)^+$ 500.1894, found 500.1907.

Benzyl (1*SR*,3a*SR*,9a*RS*)-5a-Hydroxy-2,6,11-trioxo-2,3,5,5a,6,-11-hexahydrofuro[3,2-*b*]naphtho[2,3-*c*]furan-3a-carboxylate (42). TFA (0.5 mL) was added to diol (0.1 g, 0.21 mmol) in CH_2Cl_2 (3 mL) and the solution allowed to stand for 18 h at room temperature. The solvent and TFA were evaporated in vacuo and the residue chromatographed (7:3 pentane/AcOEt) to furnish lactone **42** (0.023 g, 26%) as a white solid: IR (CH_2Cl_2) 3442, 1809, 1738, 1703, 1593, 1271 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04 (d, $J = 18.5$ Hz, 1H), 3.67 (d, $J = 18.5$ Hz, 1H), 4.15 (d, $J = 9.5$ Hz, 1H), 4.78 (d, $J = 12.0$ Hz, 1H), 4.85 (d, $J = 12.0$ Hz, 1H), 4.89 (d, $J = 9.5$ Hz, 1H), 7.09−7.32 (m, 5H), 7.74−7.85 (m, 2H), 7.98 (d, $J = 7.0$ Hz, 1H), 8.02 (d, $J = 7.0$ Hz, 1H); MS (Cl, NH_3) *m/z* 426 $(M + NH_4)^+$; HRMS (CI) *m/z* calcd for $C_{22}H_{20}NO_8$ $(M + NH_4)^+$ 426.1189, found 426.1184.

(3a*SR*,5a*RS*,11a*SR*)-5a-Hydroxy-2,6,11-trioxo-3,3a,5,5a-tetrahydrofuro[3,2-*b*]naphtho[2,3-*c*]furan-3a-carboxylic Acid (53). Ester **40** (20.0 mg, 49.0 μmol) and 10% Pd−C (2 mg) in EtOH (2 mL) and cyclohexene (0.3 mL) were heated at 80 °C for 50 min. The mixture was filtered, rotary evaporated, and chromatographed (THF) to give carboxylic acid **53** (14.2 mg, 91%) as a white solid: 161 °C dec (THF); R_f 0.30 (THF); IR (film) 3442, 1807, 1717, 1619, 1574 cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4) δ 2.17 (s, 1H), 2.92 (d, $J = 18.5$ Hz, 1H), 3.57 (d, $J = 18.5$ Hz, 1H), 4.36 (d, $J = 10.0$ Hz, 1H), 4.53 (d, $J = 10.0$ Hz, 1H), 7.85−7.93 (m, 2H), 8.10−8.13 (m, 2H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 0.7, 39.8, 53.4, 68.4, 72.5, 86.0, 87.3, 127.7, 127.8, 127.9, 128.6 (3C), 134.3, 134.7, 134.9, 135.1, 166.2, 170.5, 185.8, 190.1; LR, HR or FAB MS failed to provide usable data.

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Supporting Information Available: Additional experimental procedures and structural data for all new compounds; crystallographic data (including ORTEPs and CIFs) for compounds **19**, **21**, **24**, **28**, **38**, and **43** (CCDC 292842−292847, respectively); copies of ^{1}H NMR and ^{13}C NMR spectra for selected new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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